## REMARKS

Applicants will address each of the Examiner's objections and rejections in the order in which they appear in the Office Action

### I. Priority

In the Office Action, the Examiner is requesting a specific reference in the first sentence of the specification to the earlier applications to which benefit is claimed and the status of those earlier non-provisional applications. Applicants have amended the specification herewith to comply with this request. Accordingly, it is requested that the Examiner's objection now be withdrawn.

### II. Claim Rejections - 35 U.S.C. §112

The Examiner also rejects Claims 1-28, 30-40 and 46-50 under 35 U.S.C. §112, second paragraph, as being indefinite. This rejection is respectfully traversed.

In order to advance the prosecution of this application, Applicants have amended the claims of the present application to address the alleged informalities in claim language, as noted by the Examiner. It is respectfully submitted that these amended claims overcome each of the Examiner's enumerated objections under Section 112. Accordingly, Applicants respectfully request that this rejection be withdrawn.

### III. Scope of Enablement

The Examiner also rejects Claims 1-40 and 46-50 under 35 U.S.C. §112, first paragraph, because allegedly the specification, while being enabled for a medicament or pharmaceutical

composition which functions in combination with ionizing radiation for treating diseased cancer, infected, and lipocytic tissue, does not allegedly reasonably provide enablement for treating all other diseased tissue, such as vascular and nasal tissue, involved in coronary artery disease, myocardial infarction, and allergic reaction conditions, respectively, as an example. The Examiner further alleges that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The Examiner also contends that, while the specification provides appropriate guidance for ". . . treating cancer, lipocytic, and infected diseased tissue. . .", it is insufficient to provide guidance to enable the claimed composition ". . . to function in treating any and all human and animal tissue involving conditions affecting a majority of all organ systems." Applicants believe that this rejection is based on an improper reading of the claims, for at least the reasons outlined below and respectfully traverse this rejection.

First, the Examiner has acknowledged the remarkably broad applicability of the present invention, as described in the specification the present application of, by stating that Applicants have provided appropriate guidance that would enable one skilled in the art to use the claimed invention for "treating cancer, lipocytic, and infected diseased tissue." These three disease classes, namely cancer, obesity, and microbial infection, cover a remarkably broad portion of the spectrum of possible diseases affecting human and animal tissue. Further, the claims of the present application appropriately represent the breadth of applicability of the present invention, as demonstrated by the examples contained in the specification. Given this breadth, and the salient examples in the specification that demonstrate such breadth, Applicants respectfully submit that they have claimed an appropriate scope that is adequately enabled by the specification.

Second, the Examiner alleges that an undue amount of experimentation would be required for the skilled artisan to make and use the pharmaceutical composition, given the scope of claimed applicability. Applicants respectfully submit that any such experimentation required to practice the claimed invention is normal within the field. For example, concerning a radiosensitizer medicament of the present invention comprised, substantially of Rose Bengal, the specification states that such Rose Bengal should be contained in such radiosensitizer medicament at a concentration of "... from greater than approximately 0.001% to less than approximately 20% ..." (e.g. p. 10, lns. 12-13), and that it should be "... formulated ... in a form suitable for intracorporeal administration via various conventional modes and routes... [including] in a liquid, semisolid, solid or aerosol delivery vehicle..." (e.g. p. 15, lns. 19-21). Establishing the appropriate dosage and precise formulation for treatment of a particular disease with such a medicament is routine within the medical field, and that such level of guidance provides sufficient enablement for one of skill in the art to make and use the claimed invention, without any undue experimentation.

Augmenting these metes and bounds, Applicants have provided the skilled artisan with a number of concrete examples in the present application illustrating and teaching successful practice of the claimed invention, such as for example:

> "A specific example of ... preferential accumulation and therapeutic response of the halogenated xanthenes in diseased tissue is exhibited by Rose Bengal. In particular, the inventors of the present invention have found that Rose Bengal will accumulate preferentially in (i.e., target) some tumors and other diseased tissues. This ... is illustrated by the following examples ...:
>
> Initially, tumor cell suspensions (for example, melanoma, breast tumor, liver tumor, renal carcinoma, gall bladder tumor or prostate tumor) were injected subcutaneously into the flanks of nude mice resulting in formation of primary tumors, within a few weeks,

> at the injection site having a tumor volume of approximately 0.5-1 $cm^3$.
>
> Thereafter, a solution of Rose Bengal (for example, *≤100 μL of 10% Rose Bengal in saline*) was *intratumorally injected*, followed by *therapeutic irradiation* of the tumor within *several hours post administration using x-rays* (for example, 10 Gy at 120 keV) *or gamma rays* (for example, 4-10 Gy at 1.02 MeV). This resulted in selective destruction of tumor tissue with no substantive effect in healthy surrounding tissue." (p. 12, lns. 7-20, emphasis added)

This passage clearly teaches the skilled artisan, in accordance with the claimed invention, a successful formulation of a radiosensitizer (i.e., 10% Rose Bengal in saline); how to administer this formulation (i.e., intratumoral injection); and how and when to apply ionizing radiation (i.e., several hours post administration of the medicament) so as to treat a wide range of cancerous tumors (i.e., those of the skin, breast, liver, kidney, gall bladder and prostate). Accordingly, the skilled artisan would not be unduly burdened with experimentation in order to practice the detailed examples provided in the specification, nor to broadly extend such examples to other disease states.

Third, Applicants have, in composing the claimed scope of the present application, encompassed those tissues and disease conditions that are believed to be amenable to treatment, via radiosensitization, using the claimed radiosensitizers. For example, while it might have seemed remote in 1990 that certain forms of coronary disease would prove highly responsive to certain forms of radiation therapy, recent progress in the use of radioactive stents for control of restenosis shows that therapeutic use of radiation for treatment of coronary disease is entirely possible. Similarly, there are many other examples of diseases that appear to be amenable to treatment with radiosensitization in the future. Accordingly, the scope of the claims of the present application is consistent with both 1) the potential for such progress, 2) the proper role of the claimed invention

upon such progress, and 3) the recognition and discovery by Applicants of the claimed invention's role in such progress.

Accordingly, for at least these reasons, Applicants respectfully submit that the claims of the present application are sufficiently enabled and request that the Examiner withdraw the rejection of Claims 1-40 and 46-50 under 35 U.S.C. §112, first paragraph.

## IV. Double Patenting

The Examiner further rejects Claims 1-40 and 46-50 under the judically created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10, 14-15, 18-20, 51-52, 55-67 [sic?] and 61-67 of co-pending application no 09/382,622 and provisionally under 35 USC §103 as being obvious over co-pending application no. 09/382,622. These rejections are respectfully traversed.

However, in order to advance the prosecution of this application, Applicants are submitting herewith a terminal disclaimer to overcome the double patenting rejection.

With regard to the §103 rejection, the subject matter of the reference (i.e., USSN 09/382,622) and the claimed invention were, at the time the invention was made, owned by and/or subject to an obligation of assignment to the same entity (i.e., Photogen, Inc.)

Accordingly, it is respectfully requested that the double patenting rejections be withdrawn.

## V. Claims Rejections - 35 U.S.C. §102

### A. Rejection over Gulliya et al.

The Examiner further rejects claims 1, 5-13, 15-17, 20-22, 25-26, 28-29, 33-40 and 46-49 under 35 U.S.C. §102(b) as being anticipated by Gulliya et al. (US 5,177,073). This rejection is respectfully traversed.

In the Office Action, the Examiner alleges that Gulliya discloses a medicament that is activated by ionizing radiation. However, the claimed medicament is clearly and patentably distinct from any alleged medicament disclosed in Gulliya, for at least the reasons outlined below.

(1) Gulliya fails to disclose use of a halogenated xanthene as a component of a medicament, as required in the claimed invention.

Instead, Gulliya describes certain medicaments based on "photoactive compounds", providing the following Markush listing of these:

> "The *photoactive compounds are generally compounds, such as dyes, having one or more chromophores and capable of absorbing light energy*. The term "chromophore" refers to portions of a molecule that are fundamentally responsible for the electronic transition. These photoactive compounds can be cationic, anionic, zwitterionic, or neutral. They comprise chemical classes and their respective derivatives, including, but are not limited to: acridine, anthraquinone; azine; azo, which comprises disazo, monoazo, pyrazolones, and triazo; azomethine; carbocyanine; coumarins; diphenylmethane; flaven; flavone; flavylium salts; indigoid; methylidyne; nitro; nitroso; polymethylidyne; natural dyes such as porphyrin derivatives; psoralens; quinonimines; sulfide; sulfur; thiazole; toluidine; triphenylmethane; *xanthene*; and others. Their derivatives may contain functional groups, such as hydroxyl, carboxyl, thiol, or amino group, all of which are capable of forming chemical bonds through coupling reactions." (col. 10, lns. 26-44, emphasis added)

Thus, the compounds of Gulliya are photoactive compounds that typically absorb optical energy (i.e., "light energy"). Included in this list of light-absorbing compounds is a "xanthene" chemical class. Notably, however, Gulliya fails to use the term "halogen" (or any derivation thereof, such as halogenated, etc.) anywhere in the specification, claims, or cited references. Thus, Gulliya fails to disclose the specific, separate chemical class, of the "halogenated xanthenes", that are the subject of the claims of the present application.

In contrast to the disclosure in Gulliya, the specification of the present application clearly defines the halogenated xanthenes, such as for example:

> "The inventors of the present invention have discovered a class of radiodense agents ... referred to as *halogenated xanthenes* and are illustrated in Figure 1a, where the symbols X, Y, and Z represent various elements present at the designated positions, and the symbols $R^1$ and $R^2$ represent various functionalities present at the designated positions. The *halogen content* of the halogenated xanthenes makes this class of agent *highly efficient absorbers of x-rays or other ionizing radiation* of energy greater than approximately 1 keV and less than approximately 1000 MeV, and thus suitable as radiodense components in various radiosensitizer medicaments used in conjunction with such radiation in high energy phototherapy.
>
> "Selected chemical and physical properties (such as chemical constituents at positions X, Y, and Z and functionalities $R^1$ and $R^2$, along with molecular weight) of representative halogenated xanthenes are summarized in attached Table 1 (*infra*)." (p. 9, lns. 5-17, emphasis added)

Further, a review of the data contained in Table 1 of the specification shows, that all of the halogenated xanthenes contain one or more halogen atom, as reflected in the name of the chemical class. It is this halogen content that makes the halogenated xanthenes efficient absorbers of x-rays and other ionizing radiation. The parent compound for this chemical class, fluorescein, is listed at

the top of Table 1 for reference. The identity of the halogenated xanthenes is further defined by the following passage from the application:

> "One preferred embodiment ... contains a radiodense ingredient ... comprised of at least one *halogenated xanthene*, including for example one or more of: 4',5'-Dichlorofluorescein; 2',7'-Dichlorofluorescein; 4,5,6,7-Tetrachlorofluorescein; 2',4',5',7'-Tetrachlorofluorescein; Dibromofluorescein; Solvent Red 72; Diiodofluorescein; Eosin B; Eosin Y; Ethyl Eosin; Erythrosin B; Phloxine B; Rose Bengal (4,5,6,7-tetrachloro-2',4',5',7'-tetraiodofluorescein; shown in Figure 1b); 4,5,6,7-Tetrabromoerythrosin; Mono-, Di-, or Tribromoerythrosin; Mono-, Di-, or Trichloroerythrosin; Mono-, Di-, or Trifluoroerythrosin; 2',7'-Dichloro-4,5,6,7-Tetrafluorofluorescein; 2',4,5,6,7,7'-Hexafluorofluorescein; and 4,5,6,7-Tetrafluorofluorescein. Since the radiation cross-section of halogens increases substantially in the order F < Cl < Br < I (as shown in Figure 2), it is further preferred that this medicament include, as a radiodense ingredient, those *halogenated xanthenes with a large content of I or Br.*" (p. 10, lns. 11-22, emphasis added)

Thus, all of the claimed halogenated xanthenes contain one or more halogen atoms, and it is preferred that such halogens include the more radiodense halogens, i.e. iodine or bromine. This is further reinforced by Claims 5 and 33, which contain Markush lists describing these claimed halogenated xanthenes.[1]

Accordingly, since Gulliya makes only a passing reference to "xanthenes" and fails to disclose any of the halogenated xanthenes (or any halogenated compound whatsoever), while the

[1]"Fluorescein" was inadvertently included in Claims 5 and 33, as initially filed. However, as is clear from the sections of the specification cited supra, fluorescein does not belong in this chemical class. As such, Claims 5 and 33 have been amended to be in conformance with the specification, see especially p. 10, lns. 11-22.

present application describes and claims medicaments based on the halogenated xanthenes, it is respectfully submitted that Gulliya fails to disclose the claimed halogenated xanthenes.[2]

(2) Gulliya fails to disclose any use of radiosensitization.

The disclosure in Gulliya is directed to a "pre-activated" compound that cannot, by definition comprise a radiosensitizer. This is clearly shown by the following passages from Gulliya, beginning with the Abstract:

> "A therapeutic composition derived from a *pre-activated photoactive compound* and a conveyor for destroying tumor or other pathogenic biological contaminants infecting animal body tissues. The conveyor can either be a matrix support or an antibody. The activation of the photoactive compound to *produce the pre-activated photoactive compound* is carried out by the use of an activating agent. The pre-activated photoactive compound retains its therapeutic activity subsequent to activation." (Abstract, emphasis added)

Thus, Gulliya is describing a compound that is pre-activated to become therapeutically active. The issue of how such pre-activation is achieved is clarified in Gulliya's Summary of the Invention:

> "According to the present invention, new therapeutic compositions are provided. The new therapeutic compositions comprise a *pre-activated photoactive compound* affixed to a conveyor.... *Prior to being brought into contact with the tissue to be treated*, a *sufficient amount of an activating agent is introduced* into the photoactive compound affixed therein *to produce a therapeutic agent or pre-activated photoactive compound.*" (col. 4, lns. 43-52, emphasis added)

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[2]Suggesting that Gulliya's disclosure of "xanthenes" anticipates, a priori, the "halogenated xanthenes" of the present application is tantamount to suggesting that a disclosure of the carbon atom anticipates any and all organic chemical compounds (which, by definition, are based on a carbon backbone); the latter contention is clearly erroneous, as is the former.

This concept of pre-activation (i.e., to produce a medicament that becomes therapeutically active upon extracorporeal activation) is further detailed in Gulliya's Detailed Description of the invention:

> "The term "*pre-activated*" as used herein denotes that the *photoactive compound is activated, sensitized, or excited outside the animal or human body*, or outside the body tissues. Thus, the term "pre-activated" denotes that the activation of the photoactive compound is accomplished away from the body tissue to be treated, away from the target tumor cells or target biological pathogenic contaminants. Hence, the *activation step in the "pre-activated" method is carried out before, not after, the photoactive compound has interacted with the target tumor cells* or with other pathogenic biological contaminants. In fact, the activation step in the "pre-activated" method is carried out prior to the photoactive compound has been brought into contact with the tissue to be treated. There is no requirement for further activation at the target sites once the photoactive compound has been pre-activated. The therapeutic agent so generated has a measurable and clinically useful shelf life time. (col. 9, lns. 38-56, emphasis added)

Clearly, this passage describes pre-activation as occurring ex vivo, prior to administration of the medicament. Gulliya's method of pre-activation is further elucidated by the following:

> "Generally, a stock solution of the pre-activated therapeutic agent is prepared by dissolving an appropriate concentration of photoactive compound in an appropriate pharmaceutically acceptable carrier or vehicle as defined above. The resultant solution is *then subjected to a sufficient amount of activating agent to produce a therapeutic agent* such that the photoactive compound dissolved therein is activated and subsequently, in the absence of the activating agent, capable of interacting with, and destroying, tumors or other pathogenic biological contaminants infecting the body tissues. *Aliquots* of the stock solution *are then removed and diluted with appropriate pharmaceutically acceptable carrier or vehicle to the desired concentrations*." (col. 13, lns. 12-25, emphasis added)

> "*Pre-activated therapeutic solutions* with the desired concentration *can then be used* for either the in vitro or the in vivo application. In the in vitro application, solution containing the

> appropriate concentration of the *pre-activated therapeutic agent is administered into body tissue* or cells outside the animal body, such as human body.... In the *in vivo application*, the solution containing the appropriate concentration of *pre-activated therapeutic agent is directly administered into the animal body*. This application is useful, for example, for the treatment of animal, such as human, infected with tumor or other pathogenic biological contaminants." (col. 13, lns. 35-54, emphasis added)

Thus, Gulliya's pre-activation occurs prior to treatment (i.e., pre-activation is performed ex vivo to yield an "active" medicament). This is clearly distinct from the radiosensitization of the present inention, wherein an essentially inert (i.e., non-therapeutically active) therapeutic agent (i.e., a radiosensitizer) is delivered to diseased tissue, in vivo, and then "activated" within that tissue by subsequent application of ionizing radiation to such tissue.

Moreover, in further contrast to radiosensitization (which is predicated on use of a medicament that potentiates the therapeutic properties of *ionizing radiation* when such radiation is applied to diseased tissue containing such radiosensitizer medicament), Gulliya is principally concerned with certain uses of visible light (i.e., *non-ionizing radiation*), as illustrated by the following passages:

> "Some of the *preferred activating agents include*, but are not limited to: radiation in the entire absorption spectrum or region of the photoactive compound, preferably around the relatively strong or near maximum absorption regions of the molecules; *gamma rays*; electrons generated by an electropotential device; and chemical.
>
> "*Any suitable source can be employed* to irradiate the photoactive compound, *provided such source produces sufficient radiation to activate the photoactive compound* and to provide the resultant therapeutic agent or mixture with the desired properties mentioned above. *The operable source* employed to irradiate the resulting fluid has a *wavelength of from about 230 nm to about 1200 nm* ...." (col. 13, ln.55 - col. 14, ln. 1, emphasis added)

Thus, Gulliya's preferred mode of activation is based on use of optical radiation (i.e., that produced by an "operable source" emitting light with a wavelength from about 230 nm to about 1200 nm); any role of ionizing radiation (gamma rays) is unclear from these passages, but is unambiguously delineated by the following:

> "Because the *pre-activation* of the therapeutic agent, or the activation of the photoactive compound, *takes place before, not after nor during, the agent or compound is brought into contact with tissues*, extracorporeally or outside the body, the *activating agent used can even be a potentially lethal or dangerous radiation, such as UV or gamma rays. The UV or gamma rays used to activate the photoactive compound will not be in contact with any body tissue*. Hence, they will not harm the body tissues or the host, such as the human subject or patient." (col. 14, lns. 7-17, emphasis added)

Thus, Gulliya teaches away from the core concept of the present invention by proclaiming a need to avoid application of ionizing radiation to the patient (characterizing such radiation as "potentially lethal or dangerous" that must be precluded from contact with any body tissue). This perspective is in stark contrast to the teachings of the present application, which use medicaments (i.e., radiosensitizers) substantially comprised of one or more halogenated xanthene to potentiate the therapeutic effects of ionizing radiation upon application of such ionizing radiation to the body.

Applicants note that Gulliya mentions the possibility of activating agents after application to the body, for example:

> "The term "*post-activated*," as opposed to "pre-activated," as used herein denotes that the photoactive compound is *activated, sensitized or excited in the presence of the target body tissues, or inside the animal or human body*. Thus, the activating step in the "post-activated" method is carried out after the photoactive compound has been brought into contact with the body tissue to be treated, or after the photoactive compound has been administered into the animal body." (col. 9, lns. 57-65, emphasis added)

However, given Gulliya's adamant statements concerning the importance of avoidance of exposure of any body tissue to ionizing radiation, as discussed supra, this brief recital in the disclosure cannot be considered a disclosure of any radiosensitizer or radiosensitization.

Accordingly, since Gulliya not only fails to disclose any use of halogenated xanthenes as radiosensitizers but instead actually teaches away from the entire field of radiosensitization, Gulliya fails to disclose or suggest the claimed halogenated xanthenes as radiosensitizers, as recited in the claims of the present application.

(3) Gulliya requires complex conjugate agents not required by the present invention.

The disclosure of Gulliya is not only directed to a "pre-activated" compound but also one that is attached to a "conveyor", as described in the Abstract:

> "A therapeutic composition derived from a *pre-activated photoactive compound and a conveyor* for destroying tumor or other pathogenic biological contaminants infecting animal body tissues. The conveyor can either be a matrix support or an antibody. The activation of the photoactive compound to produce the pre-activated photoactive compound is carried out by the use of an activating agent. The pre-activated photoactive compound retains its therapeutic activity subsequent to activation." (Abstract, emphasis added)

Any doubt that the therapeutic agent in Gulliya is a conjugate agent is dispelled by the Summary of Invention, which states:

> "According to the present invention, new therapeutic compositions are provided. The new therapeutic compositions comprise a *pre-activated photoactive compound affixed to a conveyor*. The conveyor can be either a matrix support or a target-specific antibody." (col. 4, lns. 43-47, emphasis added)

Further, every independent claim of Gulliya is consistent with this conjugate-based therapeutic composition:

> "Claim 1. A therapeutic composition comprising:
> a conveyor; and
> a pre-activated photoactive compound affixed to said conveyor ...."
>
> "Claim 7. A therapeutic composition comprising:
> a conveyor;
> a photoactive compound affixed to said conveyor ...."
>
> "Claim 16. A therapeutic composition comprising:
> a matrix support, and
> a pre-activated photoactive compound covalently affixed to said matrix support ...."
>
> "Claim 18. A therapeutic composition comprising:
> sepharose beads, and
> a carbocyanine compound covalently coupled to said sepharose beads."
>
> "Claim 21. A therapeutic composition comprising:
> an antibody, and
> a pre-activated photoactive compound covalently coupled to said antibody...."
>
> "Claim 25. A therapeutic composition comprising:
> a conveyor;
> a photoactive compound covalently coupled to said conveyor...."

In contrast, the present invention bears no such cumbersome requirement. Instead, the radiosensitizer compound may be used without further complication (such as attachment to a targeting moiety, such as an antibody or matrix support, as required by Gulliya). The specification of the present application makes this clear:

> "As an example of these desirable chemical, biochemical, and physical properties, the inventors have found that the prototypical halogenated xanthene, Rose Bengal, will accumulate preferentially in (i.e. target) some tumors and other diseased tissues and pathogens, has negligible dark cytotoxicity, high light cytotoxicity upon

> illumination with visible light, relatively low cost, and the ability to clear rapidly from the body." (p. 7, lns. 18-22)

Thus, the specification teaches that the halogenated xanthenes exhibit intrinsic targeting properties, and may therefore be used without resorting to additional targeting methods. Further, the specification makes it clear that the use of conjugate methods *can* be beneficial, but merely as a way to further improve the already favorable pharmacokinetic properties of the halogenated xanthenes, as described by the following passage:

> "...the facility with which the halogenated xanthenes target specific tissues or other sites *can be further optimized* by attachment of specific functional derivatives at positions $R^1$ and $R^2$, so as to change the chemical partitioning or biological activity of the agent. For example, attachment of one targeting moiety or more at positions $R^1$ or $R^2$ can be used to improve targeting to specific tissues, such as cancerous tumor tissues or sites of localized infection. An example of this is esterification at position $R^1$ with a short aliphatic alcohol, such as n-hexanol, to produce a derivatized agent exhibiting enhanced partitioning into lipid-rich tumor tissues." (p. 8, lns. 1-7, emphasis added)

Thus, while Gulliya *requires* use of conjugate agents, these passages teach that the halogenated xanthenes are useful as therapeutic agents, as claimed in independent Claims 1, 16, 22, 29, 46 and 47 in the present application, in their simple, native (i.e., non-conjugated) form. It is only as an additional refinement that conjugation is taught. Notably, Gulliya does not teach any such non-conjugated use of any halogenated xanthene (nor of any other therapeutic moiety).

Accordingly, since Gulliya both fails to disclose any use of halogenated xanthenes as non-conjugated therapeutic agents, and in fact, teaches away from use of non-conjugated agents, Gulliya fails to disclose or suggest the present application's claimed halogenated xanthenes.

Therefore, for at least the above-stated reasons, the rejected claims are clearly note disclosed or suggested by Gulliya but are patentable thereover. Hence, it is respectfully requested that this rejection be withdrawn.

**B. Rejection Over Serafini**

The Examiner also rejects Claims 1, 3, 5, 8-12, 15-18, 20, 22-23, 25, 28-29, 31, 33, 36-39 and 46-48 and 50 under 35 U.S.C. §102(b) as being anticipated by Serafini et al.

This rejection is also respectfully traversed. In particular, the Examiner alleges that Serafini discloses: 1) "rapid and efficient incorporation into molecules so as to attain overall reduction in imaging time and radiation exposure" and 2) "improved images". The Examiner also alleges that Serafini uses Rose Bengal "... for treating diseased tissue as a radiopharmaceutical agent." Applicants vigorously dispute this interpretation of Serafini, along with the relevance thereof, for at least the reasons discussed below.

(1) Reduction in imaging time and associated radiation exposure is not relevant to radiosensitization.

The Examiner contends that Serafini discloses "rapid and efficient incorporation into molecules so as to attain overall reduction in imaging time and radiation exposure." Applicants do not understand the Examiner's statement regarding "rapid and efficient incorporation into molecules," nor its relevance. With regard to the second half of the statement, that Serafini teaches a diagnostic use of Rose Bengal, for which the "overall reduction in imaging time and radiation exposure" is relevant, Applicants disagree.

A diagnostic use of Rose Bengal is not relevant to a radiosensitizer for treatment. By definition, a diagnostic agent is used to detect or characterize a diseased state. In contrast, a radiosensitizer is used to treat a diseased state. The two are not the same, and in most cases the tools used for such are not the same, either. The following example illustrates this important distinction:

By combining an x-ray source with a detection device, one can produce an *x-ray imaging system*, such as a fluoroscope or CT imaging system. Such a system would be used routinely for diagnosis of disease, but is not suitable for treatment of disease, even if the diagnosed disease (such as a cancerous tumor) is to be treated with x-rays. It is only when the x-rays are produced by a specialized source, and delivered in a controlled manner to the diseased tissue, that one has created a *therapeutic x-ray system*. While both systems may utilize the same x-ray energy, and share many other superficial similarities, clearly they are not the same device, nor are they used for the same purpose.

Similarly, Serafini describes a diagnostic use of Rose Bengal, but Applicants have, even upon very thorough study of Serafini, failed to find any disclosure of any therapeutic use. Accordingly, Serafini's diagnostic use of Rose Bengal is completely different from the treatment claimed in the present application and therefore does not anticipate the claims herein.

(2) Serafini requires a special form of Rose Bengal that contains radioactive isotopes of iodine, while the present invention does not require such radioactive forms.

The diagnostic agents described by Serafini are comprised of forms of Rose Bengal in which the normal, non-radioactive iodine atoms have been replaced with $^{131}I$ or $^{125}I$, both of which are highly radioactive isotopes of iodine. The Examiner acknowledges this point with the statement that

"the radiopharmaceutical agent is observed with marked improvement in anatomical detail showing specific areas of radioactive concentrations." A radiopharmaceutical is, by definition, a radioactive pharmaceutical. Thus, the diagnostic agents described by Serafini are radioactive, and as noted by the Examiner, yield hazardous concentrations of radioactivity in certain tissues of the body (most notably the liver).

In contrast, the radiosensitizer agents described and claimed in the present application are non-radioactive. Being non-radioactive, they are intrinsically safe with respect to incidental radiation exposure (note that the agents in Serafini are designed to minimize radiation exposure occurring from the agent itself, but they cannot eliminate such exposure otherwise they would no longer function). The properties of the claimed radiosensitizers are described in the specification of the present application, for example, in the following terms:

> "In general, the halogenated xanthenes are characterized by a large radiation absorbance cross-section, *low dark cytotoxicity* (toxicity to cells or tissues in the absence of radiation), high light cytotoxicity (toxicity to cells or tissues upon irradiation) ... The halogenated xanthenes also exhibit a preference for concentration in diseased tissue, and thus are capable of exhibiting enhanced *radiation dose enhancement* over that possible with previously known agents." (p. 9, ln. 23 - p. 10, ln. 7, emphasis added)

Thus, Applicants' claimed Rose Bengal has low toxicity (i.e., including radiotoxicity), and instead of emitting radiation (as is the case of the radioactive form of Rose Bengal utilized by Serafini), it is used to capture or otherwise interact therapeutically with *applied radiation.* Accordingly, the diagnostic Rose Bengal disclosed in Serafini is not only functionally different from Applicants' therapeutic Rose Bengal, but it is in fact an *isotopically different compound.*

(3) As medical products, the diagnostic agent in Serafini is distinctly different from the claimed radiosensitizers.

Not withstanding the aforementioned reasons that differentiate the claimed radiosensitizer from the diagnositic radiopharmaceutical disclosed in Serafini, even if the two Rose Bengal agents were, arguendo, chemically and isotopically identical and formulated in identical forms, they would still comprise patentably distinct products (each of which is also patentably distinct from any other products containing Rose Bengal). This should be clear after (a) examining the definition of the claimed radiosensitizer and (b) considering the position of such a radiosensitizer within the commercial realm.

First, the present application is directed to and discusses radiosensitizers (i.e., therapeutic medicaments) that include one or more halogenated xanthenes. The term "radiosensitizer" is used consistently throughout the specification in such a way that makes it clear that such agents are used to enhance the therapeutic efficacy of applied ionizing radiation. For example, the specification defines "radiosensitizers" early in the application:

> "... some investigators have focused their efforts on developing agents that become activated by, or *increase the therapeutic potential of*, such *ionizing radiation*. Such agents are known as *radiosensitizers*, and when used in combination with ionizing radiation constitute a therapeutic modality known as high energy phototherapy. Since radiosensitizers function by absorbing or otherwise interacting with penetrating, ionizing radiation and locally transforming this radiation into a more biologically active form, it is desirable that such radiosensitizer agents exhibit high intrinsic radiodensity and a capacity for preferential concentration in diseased tissue (thus allowing maximal, selective delivery of the therapeutic effects of such radiation to such diseased tissue containing such agent)." (p. 2, ln. 22 - p. 3, ln. 7, emphasis added)

Thus, radiosensitizers are therapeutic agents that increase the therapeutic potential of ionizing radiation. The mechanism of these radiosensitizers is further described, for example, by the following passage:

> "The therapeutic performance of a radiosensitizer is a function of *enhanced absorption of the applied radiation dose* in sensitized tissues relative to that in non-sensitized tissues. This differential absorption is commonly effected by use of radiodense agents having a high absorption cross-section for a particular type of radiation (such as x-rays). For example, metal or halogen atoms are often used, either in atomic form or incorporated into a molecular carrier, due to their high x-ray cross-section. Absorption of x-rays by such radiodense materials appears to lead to secondary radiative emissions, ionization, and other chemical or physical processes that *increase the localized cytotoxicity* of the applied energy (i.e., radiation-induced cell death, or "light cytotoxicity")." (p. 3, ln. 19 - p. 4, ln. 3, emphasis added)

Thus, the specification defines radiosensitizers as therapeutic agents that locally enhance the absorption of applied radiation so as to increase the localized cytotoxicity of such radiation in treated tissues. The fundamental basis for the radiosensitizers claimed in the present application is described by the following passage, which not only identifies the halogenated xanthenes as the primary active component of such radiosensitizers, but also explains why such halogenated xanthenes are suitable for such use:

> "The inventors of the present invention have discovered a *class of radiodense agents* that are broadly applicable for producing intracoporeal medicaments for high energy phototherapeutic treatment of disease in certain human and animal tissues. These radiodense agents are referred to as *halogenated xanthenes*.... The *halogen content* of the halogenated xanthenes makes this class of agent *highly efficient absorbers* of x-rays or other ionizing radiation of energy greater than approximately 1 keV and less than approximately 1000 MeV, and thus *suitable as radiodense components in various radiosensitizer medicaments* used in

> conjunction with such radiation in high energy phototherapy. (p. 9 lns. 5-14, emphasis added)

Thus, this passage teaches that the halogenated xanthenes, by virtue of their halogen content, are highly efficient absorbers of applied radiation and are thereby suitable for use as a radiation absorbing component of a radiosensitizer medicament. Thus, in distinct contrast to the teachings in Serafini (which concern certain diagnostic agents), the claimed invention concerns therapeutic agents.

Second, again even if one were to assume arguendo that the diagnostic agent disclosed in Serafini containing Rose Bengal and the therapeutic medicament of the present invention (also containing Rose Bengal) were physically identical (i.e., chemically and isotopically identical and formulated in identical forms), such materials would be nonetheless patentably distinct because, being medical products, they would have separate commercial identities and channels of commerce. This is clearly the case because the U.S. Food and Drug Administration ("FDA") strictly regulates interstate commerce in all such medical products (including both diagnostic agents and medicinal drugs) for human use in the U.S.

For instance, the FDA has detailed labeling requirements concerning identification of the manufacturer, directions for use, ingredients, and intended use for any medical product sold in interstate commerce. For example, concerning identification of manufacturer, 21 CFR §201.1 ("Drugs; name and place of business of manufacturer, packer, or distributor") states:

> "(a) A drug or drug product ... in finished package form is misbranded ... if its label does not bear conspicuously the name and place of business of the manufacturer, packer, or distributor..."

Further, 21 CFR §201.5 ("Drugs; adequate directions for use") requires detailed labeling concerning intended usage and dosage:

> "*Adequate directions for use* means directions under which the layman can use a drug safely and for the purposes for which it is intended. (Section 201.128 defines "intended use.") Directions for use may be inadequate because, among other reasons, of omission, in whole or in part, or incorrect specification of:
>
> (a) Statements of all conditions, purposes, or uses for which such drug is intended, including conditions, purposes, or uses for which it is prescribed, recommended, or suggested in its oral, written, printed, or graphic advertising, and conditions, purposes, or uses for which the drug is commonly used; except that such statements shall not refer to conditions, uses, or purposes for which the drug can be safely used only under the supervision of a practitioner licensed by law and for which it is advertised solely to such practitioner.
>
> (b) Quantity of dose, including usual quantities for each of the uses for which it is intended and usual quantities for persons of different ages and different physical conditions.
>
> (c) Frequency of administration or application.
>
> (d) Duration of administration or application.
>
> (e) Time of administration or application (in relation to time of meals, time of onset of symptoms, or other time factors).
>
> (f) Route or method of administration or application.
>
> (g) Preparation for use, i.e., shaking, dilution, adjustment of temperature, or, other manipulation or process." (Emphasis in original)

Thus, the FDA mandates labeling that makes intended use clear even to the layman. Moreover, the FDA also strictly regulates the quantitative, definitive identification of drug ingredients; 21 CFR §201.10 ("Drugs; statement of ingredients") states:

> "(a) The ingredient information ... shall appear together, without any intervening written, printed, or graphic matter, ....
>
> (b) The term *ingredient* applies to any substance in the drug, whether added to the formulation as a single substance or in admixture with other substances..." (Emphasis in original)

Finally, concerning intended use (i.e., indications) for a drug, 21 CFR §201.128 ("Meaning of 'intended uses' ") states:

> "The words *intended uses* or words of similar import ... refer to the objective intent of the persons legally responsible for the labeling of drugs. The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives." (Emphasis in original)

Therefore, any drug product, such as a radiosensitizer agent or a medical diagnostic agent, is, within all jurisdictions of the U.S. (i.e., all jurisdictions falling under the auspices of the U.S. FDA, as well as those of the U.S. PTO), strictly regulated by the FDA, and requires detailed labeling concerning manufacturer, composition and intended use.

The manufacturer is legally responsible for assuring compliance with these FDA requirements.

As such, these FDA requirement assure that the commercial channels for any radiosensitizer claimed in the present application are clearly and patentably distinct from those of a diagnostic agent, such as that described in Serafini, that is based upon Rose Bengal.

Moreover, the commercial channels for both of these "drugs" are clearly and patentably distinct from those of any non-drug product (such as reagent grade Rose Bengal from a chemical supply house, such as for example Sigma Chemical, that is used for laboratory, industrial or cosmetic purposes). Since the FDA requires that a radiosensitizer based on the present invention must be labeled for its intended use (i.e., as a radiosensitizer) and identify its manufacturer (i.e., identify the Applicant or licensee of the Applicants' claimed invention), it would be clear to the layman (i.e., 21 CFR §201.5 requires labeling sufficient that "the layman can use [the product] safely and

[understand] the purposes for which it is intended") that such radiosensitizer was distinctly different from any other extant or future product.

Finally, it is important to note that due to these FDA regulations, a hypothetical radiosensitizer medicament comprised, for example, of pure Rose Bengal, is not "Rose Bengal" but rather the regulated medicament (i.e., the radiosensitizer). As such, it cannot be sold for any other commercial purpose, nor represented as comprising any other product, such as, for example, the diagnostic agent described by Serafini or reagent-grade Rose Bengal sold by Sigma.

Accordingly, Applicants' claimed radiosensitizer is patentably distinct from all other medical and non-medical products containing Rose Bengal or any other halogenated xanthene. Granting of Applicants' claims to such radiosensitizer will in no way impact these other commercial channels nor lead to confusion among those working in the respective fields utilizing such channels of commerce.

For at least the aforementioned reasons, Applicants respectfully submit that the rejected claims of the present application are clearly distinguishable and patentable over Serafini and should be allowed. Accordingly, it is requested that this rejection now be withdrawn.

### C. Rejection Over Neckers

The Examiner also rejects claims 1, 3, 5, 8-10, 12, 16, 18, 20, 22-23, 25, 28-29, 31, 33, 36-39 and 46-48 and 50 under 35 U.S.C. §102(b) as being anticipated by Neckers. This rejection is also respectfully traversed.

In particular, the Examiner alleges that Neckers discloses: 1) "halogenated xanthenes such as Rose Bengal"; 2) "that Rose Bengal and Eosin have distinct spectral, photochemical, and

photophysical properties"; 3) that Rose Bengal [is] "a photodynamic sensitizer" having a "large absorption in all solvents," a "capacity to be activated as an imaging agent," and "a triplet that is completely quenched by oxygen;" 4) that Rose Bengal exhibits "concentration on selected tissues, i.e., tumor;" 5) that the spectrum of Rose Bengal "is most diagnostic of its immediate environment;" 6) that Rose Bengal exhibits "bleaching in protic, polar solvents"; and that 7) "its singlet is quenched by strong oxidizing agents." Applicants respectfully submit that these issues are not relevant to the present invention, as described below.

As discussed in detail supra, the present invention concerns certain uses of halogenated xanthenes in radiosensitizer medicaments. In this capacity, such medicaments enhance the therapeutic effect of applied *ionizing radiation*. The useful range of such radiation is defined in the specification of the present application, for example, by the following:

> "Diseased tissue or tumors, such as those of cancer, are often treated using high energy, highly penetrating *ionizing radiation* (i.e., ionizing radiation, or radiation), in a process known as radiation therapy.
>
> "Conventional radiation therapy (which typically *uses ionizing radiation with energies of 1 keV or higher*) generally works by attacking rapidly growing cells with ionizing radiation. Use of such radiation is attractive due to its ability to penetrate deeply into tissue, especially when diseased tissue consists of, or is located within, bone or other dense or opaque structures." (p. 2, lines 7-13, emphasis added)
>
> "The halogen content of the halogenated xanthenes makes this class of agent highly efficient *absorbers of x-rays or other ionizing radiation of energy greater than approximately 1 keV and less than approximately 1000 MeV*, and thus suitable as radiodense components in various radiosensitizer medicaments *used in conjunction with such radiation* in high energy phototherapy." (p. 9, lns. 10-14, emphasis added)

Thus, the subject of the present application concerns the properties of, and certain uses for, the halogenated xanthenes when such halogenated xanthenes are irradiated with ionizing radiation having energies of 1 keV or higher. An energy of 1 keV or higher corresponds to a wavelength of 0.0012 nm or shorter.

In contrast, Neckers thoroughly describes the properties of the halogenated xanthenes with regard to *optical radiation* (i.e., having wavelengths equal to at least about 100 nm or greater). The Examiner will note that Neckers' discussion of the properties of the halogenated xanthenes concerning their:

- distinct spectral, photochemical, and photophysical properties,
- photodynamic sensitizer properties,
- absorption properties in certain solvents,
- use as a fluorescent imaging agent,
- triplet state quenching,
- effects of the immediate environment on spectral properties,
- photobleaching in protic, polar solvents, and
- singlet quenching by strong oxidizing agents

all pertain to phenomena observed only with, and relevant only to, their interaction with optical radiation.

Specifically, Neckers discloses none of the properties of any halogenated xanthene relevant to irradiation with ionizing radiation having energies of 1 keV or higher.

Applicants have been unable to identify the Examiner's alleged disclosure by Neckers that Rose Bengal exhibits "concentration on selected tissues, i.e., tumor", and the Examiner has not

identified where this is allegedly disclosed. However, such disclosure would be irrelevant to the present invention, since Neckers fails to predict any useful interaction of ionizing radiation with Rose Bengal (or any other halogenated xanthene), and thus cannot disclose or predict the radiosensitizer medicaments of the claimed invention.

Therefore, for at least the above-stated reasons, it is respectfully submitted that Neckers fails to disclose or suggest the claimed invention, and that the claims of the present application are patentable thereover. Accordingly, it is requested that this rejection be withdrawn.

Therefore, for at least the above-stated reasons, it is respectfully requested that each of the §102 rejections be withdrawn.

## VI. Claim Rejections - 35 U.S.C. §103

### A. Rejection Over Gulliya

The Examiner also rejects claims 2, 27 and 30 under 35 U.S.C. §103(a) as being unpatentable over Gulliya et al. (US 5,177,073). This rejection is also respectfully traversed. In particular, the Examiner alleges that Gulliya discloses a "medicament [that] is activated by application of ionizing radiation." For at least the reasons discussed above for a similar rejection of the independent claims upon which Claims 2, 27 and 30 are based, Gulliya does not disclose or suggest the claimed invention, and Applicants respectfully request that this rejection be withdrawn.

More specifically, as presented supra, Gulliya describes certain medicaments that are "pre-activated" by application of energy prior to their administration. In contrast, the claimed invention concerns certain other medicaments that are administered prior to application of energy (i.e., ionizing radiation). Clearly, these are not the same medicaments. Furthermore, insofar that Gulliya describes

any use of ionizing radiation, this is clearly presented as a form of energy that is to be kept completely away from living tissue (Gulliya characterizes such radiation as "potentially lethal or dangerous" and warns that it should be precluded from contact with any body tissue). Thus, Gulliya mentions pre-activation of agents disclosed therein with such radiation prior to administration to the body. This is in stark contrast to the teachings of the present application, wherein radiosensitizer medicaments are used to potentiate the therapeutic effects of ionizing radiation upon application of such ionizing radiation to the body (in fact such radiosensitizers can only function if: (a) they are present in the body; and (b) ionizing radiation is applied to the body).

Further, as discussed supra viz-a-via the rejection over Serafini and the U.S. FDA, even if, arguendo, the physical composition of the therapeutic agent disclosed in Gulliya was identical to that of the claimed radiosensitizer, the two medicaments would nonetheless be patentably distinct. This distinction would result from their different respective "directions for use" (i.e., per 21 CFR §201.5, "Drugs; adequate directions for use"). For instance, Gulliya's medicament would require labeling along the lines of, "pre-activate prior to use," while the medicament of the claimed invention would require labeling along the lines of, "administer prior to radiation treatment." Such distinction is unambiguous.

Since the medicaments are clearly and patentably distinct, Applicants respectfully request that rejection of Claims 2, 27 and 30 under 35 U.S.C. §103(a), as being unpatentable over Gulliya, be withdrawn.

## B. Rejection Over Gulliya in View of Fondren

The Examiner also rejects claims 4, 19, 24 and 32 under 35 U.S.C. §103(a) as being unpatentable over Gulliya et al. (US 5,177,073) in view of Fondren et al. In the Office Action, the Examiner alleges that combining the teachings of Gulliya with those of Fondren would have made the claimed invention obvious. This rejection is also respectfully traversed.

As discussed supra, Gulliya describes certain medicaments that are "pre-activated" by application of energy prior to administration. Substitution of the xanthene dyes described by Fondren does not change the fact that the medicament in Gulliya is not a radiosensitizer. Since it is pre-activated, it cannot, by definition, serve as a radiosensitizer (i.e., as a medicament that enhances the local effect of applied ionizing radiation). Even assuming that these references can be combined, which Applicants do not admit, one of skill in the art still would not be led to the claimed radiosensitizer, since even if, upon reading Fondren one was inspired to use Rose Bengal as a component of the agent in Gulliya, one certainly would not administer the agent and then apply ionizing radiation to the body (as required of a radiosensitizer), since Gulliya unambiguously warns against such application of ionizing radiation.

Since Gulliya clearly teaches away from the claimed invention, and the addition of Fondren fails to cure the notable shortcomings of reference, the hypothetical combination of Gulliya with Fondren cannot arrive at the claimed invention. For at least this reason, the claimed invention is patentable over the cited references, and Applicants respectfully request that the rejection of Claims 4, 19, 24 and 32 under 35 U.S.C. §103(a), as being unpatentable over Gulliya in view of Fondren be withdrawn.

## C. Rejection Over Gulliya or Neckers in View of Norman

The Examiner also rejects claim 14 under 35 U.S.C. §103(a) as being unpatentable over Gulliya et al. (US 5,177,073) or Neckers in view of Norman et al. In the Office Action, the Examiner alleges that combining the teachings of Gulliya or Neckers with those of Norman would have made the claimed invention obvious. This rejection is also respectfully traversed.

As discussed in detail supra, Gulliya fails to disclose radiosensitization, and instead teaches away from such therapeutic modality. An unlikely combination of the teachings of Gulliya with those of Norman fails to cure this failing, since it would be illogical for one of skill in the art to do so: it would force the skilled artisan, on the one hand, to accept the teachings of Gulliya (which espouse "pre-activation" of photoactive therapeutic agents prior to their administration and the rigorous avoidance of any exposure of tissue to ionizing radiation), and then on the other hand to discard all such teachings so as to follow those of Norman (which teaches about post-administration irradiation of tissue with ionizing radiation). It is extremely unlikely that such artisan would go through the following process: 1) selectively choose the "xanthenes" mentioned one time by Gulliya (which are described in the context of "photoactive compounds ... such as dyes"); 2) add halogens to these cited xanthenes to arrive at a halogenated xanthene; 3) strip the required attached conjugate moiety off of this new halogenated xanthene to arrive at the non-conjugated halogenated xanthenes of the present invention; 4) declare such entities CT contrast media (i.e., contrast agents for use with ionizing radiation, as described by Norman); and 5) finally decide to use such entities therapeutically with applied ionizing radiation as radiosensitizers. Such a complex, tortured line of reasoning and multiple leaps of logic to combine references to arrive at the claimed invention seems, to Applicants, to fly in the very face of the definition of invention. Instead, this seems to be a clear example of

hindsight reconstruction of choosing select pieces from various references while choosing to ignore other teachings in the references. Such a practice is clearly improper under the law, and any rejection based thereon is also improper and should be withdrawn. Accordingly, for at least this reason, the Examiner's rejection of Claim 14 for alleged obviousness over Gulliya in view of Norman is improper and should be withdrawn.

The case for combining Neckers with Norman is nearly as tortured. For example, as described in detail supra, Neckers is concerned with the optical properties of the halogenated xanthenes. The energy band of optical energy covered by Neckers is extremely far removed from the ionizing radiation energy band described by Norman. As a consequence, the physical properties and fundament mechanisms responsible for interaction of such halogenated xanthenes with, on the one hand, the optical energy of Neckers (i.e., light) are completely unrelated to those associated with their respective interaction with the ionizing radiation of Norman. Since there is virtually no overlap between the fields of study concerning such optical energy and such ionizing radiation, it is highly unlikely that a skilled artisan would be motivated to 1) use the spectroscopic and photochemical properties described by Neckers as the basis for concluding that 2) wholly-unrelated properties in the x-ray band are relevant to potential use as CT contrast media, and then that 3) such contrast media are useful as radiosensitizers. Again, such a complex synthesis of combining references of apparently unrelated concepts across the traditional boundaries that define separate fields of study seems, to Applicants, to again fly in the face of the definition of invention. This is again improper hindsight reconstruction. Accordingly, for at least this reason, Applicants believe that the Examiner's rejection of Claim 14 for alleged obviousness over Neckers in view of Norman is improper and should be withdrawn.

Finally, it is unlikely that a skilled artisan would be motivated to selectively combine portions of the teachings of Gulliya and Neckers (neither of which concern CT contrast media or radiosensitization) with those of Norman (which fails to describe any "xanthene" or halogenated xanthene) to arrive at the claimed invention. Gulliya teaches away from the use of ionizing radiation, while Neckers is completely silent on any properties of the halogenated xanthenes outside the optical energy band, and Norman is concerned with new uses of known CT contrast agents. Any hypothetical combination of these teachings does not cross the substantial divide between the known optical properties of any such agents and the fact that such agents were not, at the time of filing of the present application, known to be useful as CT contrast agents.

Accordingly, for at least the above-stated reasons, the Examiner's rejection of Claim 14 for alleged obviousness over Gulliya or Neckers in view of Norman is improper and should be withdrawn.

Therefore, for at least the reasons discussed above, it is respectfully requested that the §103 rejections be withdrawn.

## VII. Conclusion

For at least the above-stated reasons, it is respectfully submitted that the claims of the present application are in an allowable form and are patentable over the cited references. Accordingly, it is requested that the application now be allowed.

If any fee should be due for this response, please charge our deposit account 50/1039.

Favorable reconsideration is earnestly solicited.

Respectfully submitted,

Date: April 22, 2003

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Marked-up copy of the amendments made herein:

**IN THE SPECIFICATION:**



Please amend the specification as follows:

Amend the paragraph at page 1, lns. 5-7 as follows:

This application is based on provisional application USSN 60/195,090 and a continuation-in-part of USSN 09/216,787 (entitled "High Energy Phototherapeutic Agents"), filed on December 21, 1998 (now U.S. Patent 6,331,286 issued December 18, 2001), which is herein incorporated by reference in its entirety.

**IN THE CLAIMS:**

Please amend the claims as follows:

Claim 1 (Amended). A medicament for intracorporeal application, the medicament comprising at least one halogenated xanthene as a primary active component, wherein said medicament is [useful] for high energy phototherapeutic treatment, using applied ionizing radiation, of human and animal tissue.

Claim 2 (Amended). The medicament of [Claim] claim 1 wherein said halogenated xanthene is present in a concentration of greater than about 0.001% to less than about 20%.

Claim 3 (Amended). The medicament of [Claim] claim 1 wherein said halogenated xanthene comprises Rose Bengal.

Claim 4 (Amended). The medicament of [Claim] claim 1 wherein said halogenated xanthene comprises 4,5,6,7-Tetrabromoerythrosin.

Claim 5 (Amended). The medicament of [Claim] claim 1 wherein said halogenated xanthene includes at least one compound selected from the group consisting of [Fluorescein;] 4',5'-Dichlorofluorescein; 2',7'-Dichlorofluorescein; 4,5,6,7-Tetrachlorofluorescein; 2',4',5',7'-Tetrachlorofluorescein; Dibromofluorescein; Solvent Red 72; Diiodofluorescein; Ethyl Eosin; Erythrosin B; Phloxine B; Rose Bengal; 4,5,6,7-Tetrabromoerythrosin; Mono-, Di-, or Tribromoerythrosin; Mono-, Di-, or Trichloroerythrosin; Mono-, Di-, or Trifluoroerythrosin; 2',7'-Dichloro-4,5,6,7-Tetrafluorofluorescein; 2',4,5,6,7,7'-Hexafluorofluorescein; and 4,5,6,7-Tetrafluorofluorescein.

Claim 6 (Amended). The medicament of [Claim] claim 1 further comprising at least one targeting moiety coupled to said halogenated xanthene.

Claim 7 (Amended). The medicament of [Claim] claim 6 wherein said targeting moiety is selected from the group consisting of deoxyribonucleic acid (DNA), ribonucleic acid (RNA), amino acids, proteins, antibodies, ligands, haptens, carbohydrate receptors, carbohydrate complexing agents, lipid receptors, lipid complexing agents, protein receptors, protein complexing agents, chelators, encapsulating vehicles, short-chain aliphatic hydrocarbons, long-chain aliphatic hydrocarbons, aromatic hydrocarbons, aldehydes, ketones, alcohols, esters, amides, amines, nitrites,

azides, hydrophilic moieties and hydrophobic moieties.

Claim 8 (Amended). The medicament of [Claim] claim 1 wherein said medicament is formulated in a delivery vehicle selected from the group consisting of liquids, semisolids, solids and aerosols.

Claim 9 (Amended). The medicament of [Claim] claim 8 wherein said vehicle is selected from the group consisting of aqueous suspensions, non-aqueous suspensions, solutions, creams, ointments, gels, syrups, suppositories, tablets, capsules and micro-droplet sprays.

Claim 10 (Amended). The medicament of [Claim] claim 1 wherein said halogenated xanthene is in a delivery vehicle that includes an adjuvant selected from the group consisting of builders, stabilizers, emulsifiers, dispersants, preservatives, buffers, electrolytes, tissue penetrating agents and tissue softening agents.

Claim 11 (Amended). The medicament of [Claim] claim 1 wherein said medicament is [useful] for the treatment of indications selected from the group consisting of diseases of [conditions affecting] the skin [and related organs], diseases of [conditions affecting] the mouth and digestive tract [and related organs], diseases of [conditions affecting] the urinary and reproductive tracts [and related organs], diseases of [conditions affecting] the respiratory tract [and related organs], diseases of [conditions affecting] the circulatory system [and related organs], diseases of [conditions affecting] the head and neck, diseases of [conditions affecting] the endocrine and lymphoreticular

systems [and related organs], diseases of [conditions affecting] connective tissues, diseases of [conditions affecting] tissue surfaces exposed during surgery, and diseases caused by [conditions related to] microbial, viral, fungal, and parasitic infection.

Claim 12 (Amended). The medicament of [Claim] claim 1 wherein said ionizing radiation is applied x-ray irradiation.

Claim 13 (Amended). The medicament of [Claim] claim 1 wherein said ionizing radiation is applied gamma irradiation.

Claim 14 (Amended). The medicament of [Claim] claim 1 wherein said ionizing radiation has an energy of greater than approximately 1 KeV and less than approximately 1000 MeV.

Claim 15 (Amended). The medicament of [Claim] claim 1 wherein said intracorporeal administration comprises a route of administration selected from the group consisting of intravenous injection, intraperitoneal injection, intramuscular injection, intracranial injection, intratumoral injection, intraepithelial injection, transcutaneous delivery, per oesophageal administration, intraabdominal administration, intraapendicular administration, intraarterial administration, intraarticular administration, intrabronchial administration, intrabuccal administration, intracapsular administration, intracardial administration, intracartilaginous administration, intracavitary administration, intracephalic administration, intracolic administration, intracutaneous administration, intracystic administration, intradermal administration, intraductal administration, intraduodenal

administration, intrafascicular administration, intrafat administration, intrafilar administration, intrafissural administration, intragastric administration, intraglandular administration, intrahepatic administration, intraintestinal administration, intralamellar administration, intralesional administration, intraligamentous administration, intralingual administration, intramammary administration, intramedullary administration, intrameningeal administration, intramyocardial administration, intranasal administration, intraocular administration, intraoperative administration, intraoral administration, intraosseous administration, intraovarian administration, intrapancreatic administration, intraparietal administration, intrapelvic administration, intrapericardial administration, intraperineal administration, intraperitoneal administration, intraplacental administration, intrapleural administration, intrapontine administration, intraprostatic administration, intrapulmonary administration, intrarachidian administration, intrarectal administration, intrarenal administration, intrascleral administration, intrascrotal administration, intrasegmental administration, intrasellar administration, intraspinal administration, intrasplenic administration, intrasternal administration, intrastromal administration, intrasynovial administration, intratarsal administration, intratesticular administration, intrathoracic administration, intratonsillar administration, intratracheal administration, intratubal administration, intratympanic administration, intraureteral administration, intraurethral administration, intrauterine administration, intravaginal administration, intravascular administration, intraventricular administration, intravertebral administration, intravesical administration, and intravitreous administration.

Claim 16 (Amended). Use of a halogenated xanthene as a radiodense component in the preparation of an intracorporeal medicament for high energy phototherapeutic treatment of human

and animal tissue using applied ionizing radiation.

Claim 17 (Amended). The use of [Claim] claim 16 for preparation of a medicament for the treatment of indications selected from the group consisting of diseases of [conditions affecting] the skin and related organs, diseases of [conditions affecting] the mouth and digestive tract and related organs, diseases of [conditions affecting] the urinary and reproductive tracts and related organs, diseases of [conditions affecting] the respiratory tract and related organs, diseases of [conditions affecting] the circulatory system and related organs, diseases of [conditions affecting] the head and neck, diseases of [conditions affecting] the endocrine and lymphoreticular systems and related organs, diseases of [conditions affecting] connective tissues, diseases of [conditions affecting] tissue surfaces exposed during surgery, and diseases caused by [conditions related to] microbial, viral, fungal, and parasitic infection.

Claim 18 (Amended). The use of [Claim] claim 16 wherein said halogenated xanthene comprises Rose Bengal.

Claim 19 (Amended). The use of [Claim] claim 16 wherein said halogenated xanthene comprises 4,5,6,7-Tetrabromoerythrosin.

Claim 20 (Amended). The use of [Claim] claim 16 wherein said ionizing radiation is applied ionizing radiation is x-ray irradiation.

Claim 21 (Amended). The use of [Claim] claim 16 wherein said ionizing radiation is applied ionizing radiation is gamma irradiation.

Claim 22 (Amended). Intracorporeal use of a halogenated xanthene comprising: administering a [therapeutically effective amount of a] halogenated xanthene into or proximate to human or animal tissue and irradiating the halogenated xanthene present within or proximate to said tissue with applied ionizing radiation.

Claim 23 (Amended). The use of [Claim] claim 22 wherein said halogenated xanthene comprises Rose Bengal.

Claim 24 (Amended). The use of [Claim] claim 22 wherein said halogenated xanthene comprises 4,5,6,7-Tetrabromoerythrosin.

Claim 25 (Amended). The use of [Claim] claim 22 wherein said applied ionizing radiation is x-ray irradiation.

Claim 26 (Amended). The use of [Claim] claim 22 wherein said applied ionizing radiation is gamma irradiation.

Claim 27 (Amended). The use of [Claim] claim 22 wherein said halogenated xanthene is at a concentration of greater than approximately 0.001% to less than approximately 20%.

Claim 28 (Amended). The use of [Claim] claim 22 wherein said administering comprises use of a route of administration selected from the group consisting of intravenous injection, intraperitoneal injection, intramuscular injection, intracranial injection, intratumoral injection, intraepithelial injection, transcutaneous delivery, per oesophageal administration, intraabdominal administration, intraapendicular administration, intraarterial administration, intraaricular administration, intrabronchial administration, intrabuccal administration, intracapsular administration, intracardial administration, intracartilaginous administration, intracavitary administration, intracephalic administration, intracolic administration, intracutaneous administration, intracystic administration, intradermal administration, intraductal administration, intraduodenal administration, intrafascicular administration, intrafat administration, intrafilar administration, intrafissural administration, intragastric administration, intraglandular administration, intrahepatic administration, intraintestinal administration, intralamellar administration, intralesional administration, intraligamentous administration, intralingual administration, intramammary administration, intramedullary administration, intrameningeal administration, intramyocardial administration, intranasal administration, intraocular administration, intraoperative administration, intraoral administration, intraosseous administration, intraovarian administration, intrapancreatic administration, intraparietal administration, intrapelvic administration, intrapericardial administration, intraperineal administration, intraperitoneal administration, intraplacental administration, intrapleural administration, intrapontine administration, intraprostatic administration,

intrapulmonary administration, intrarachidian administration, intrarectal administration, intrarenal administration, intrascleral administration, intrascrotal administration, intrasegmental administration, intrasellar administration, intraspinal administration, intrasplenic administration, intrasternal administration, intrastromal administration, intrasynovial administration, intratarsal administration, intratesticular administration, intrathoracic administration, intratonsillar administration, intratracheal administration, intratubal administration, intratympanic administration, intraureteral administration, intraurethral administration, intrauterine administration, intravaginal administration, intravascular administration, intraventricular administration, intravertebral administration, intravesical administration, and intravitreous administration.

Claim 29 (Amended). A pharmaceutical composition for intracorporeal administration comprising a halogenated xanthene for high energy phototherapeutic treatment using applied ionizing radiation.

Claim 30 (Amended). The pharmaceutical composition of [Claim] claim 29 wherein said halogenated xanthene is present in a concentration of greater than about 0.001% to less than about 20%.

Claim 31 (Amended). The pharmaceutical composition of [Claim] claim 29 wherein said halogenated xanthene comprises Rose Bengal.

Claim 32 (Amended). The pharmaceutical composition of [Claim] claim 29 wherein said halogenated xanthene comprises 4,5,6,7-Tetrabromoerythrosin.

Claim 33 (Amended). The pharmaceutical composition of [Claim] claim 29 wherein said halogenated xanthene includes at least one compound selected from the group consisting of [Fluorescein;] 4',5'-Dichlorofluorescein; 2',7'-Dichlorofluorescein; 4,5,6,7-Tetrachlorofluorescein; 2',4',5',7'-Tetrachlorofluorescein; Dibromofluorescein; Solvent Red 72; Diiodofluorescein; Ethyl Eosin; Erythrosin B; Phloxine B; Rose Bengal; 4,5,6,7-Tetrabromoerythrosin; Mono-, Di-, or Tribromoerythrosin; Mono-, Di-, or Trichloroerythrosin; Mono-, Di-, or Trifluoroerythrosin; 2',7'-Dichloro-4,5,6,7-Tetrafluorofluorescein; 2',4,5,6,7,7'-Hexafluorofl- uorescein; and 4,5,6,7-Tetrafluorofluorescein.

Claim 34 (Amended). The pharmaceutical composition of [Claim] claim 29 further comprising at least one targeting moiety coupled to said halogenated xanthene.

Claim 35 (Amended). The pharmaceutical composition of [Claim] claim 34 wherein said targeting moiety is selected from the group consisting of deoxyribonucleic acid (DNA), ribonucleic acid (RNA), amino acids, proteins, antibodies, ligands, haptens, carbohydrate receptors, carbohydrate complexing agents, lipid receptors, lipid complexing agents, protein receptors, protein complexing agents, chelators, encapsulating vehicles, short-chain aliphatic hydrocarbons, long-chain aliphatic hydrocarbons, aromatic hydrocarbons, aldehydes, ketones, alcohols, esters, amides, amines, nitrites,

azides, hydrophilic moieties and hydrophobic moieties.

Claim 36 (Amended). The pharmaceutical composition of [Claim] claim 29 wherein said pharmaceutical composition is formulated in a delivery vehicle selected from the group consisting of liquids, semisolids, solids and aerosols.

Claim 37 (Amended). The pharmaceutical composition of [Claim] claim 36 wherein said vehicle is selected from the group consisting of aqueous suspensions, non-aqueous suspensions, solutions, creams, ointments, gels, syrups, suppositories, tablets, capsules and micro-droplet sprays.

Claim 38 (Amended). The pharmaceutical composition of [Claim] claim 29 wherein said halogenated xanthene is in a delivery vehicle that includes an adjuvant selected from the group consisting of builders, stabilizers, emulsifiers, dispersants, preservatives, buffers, electrolytes, tissue penetrating agents and tissue softening agents.

Claim 39 (Amended). The pharmaceutical composition of [Claim] claim 29 wherein said applied ionizing radiation is x-ray irradiation.

Claim 40 (Amended). The pharmaceutical composition of [Claim] claim 29 wherein said applied ionizing radiation is gamma irradiation.

Claim 46 (Amended). An intracorporeally-applicable medicament comprising at least one halogenated xanthene as a primary active component, wherein said [such] medicament is [useful] for high energy phototherapeutic treatment, using applied ionizing radiation, of human and animal tissue.

Claim 47 (Amended). A pharmaceutical composition [adapted] for intracorporeal administration [to obtain a high energy phototherapeutic effect,] comprising a dosage unit of a halogenated xanthene suitable for radiosensitization using [and an effective amount of] applied ionizing radiation.

Claim 48 (Amended). The pharmaceutical composition of [Claim] claim 47 wherein said applied ionizing radiation is x-ray irradiation.

Claim 49 (Amended). The pharmaceutical composition of [Claim] claim 47 wherein said applied ionizing radiation is gamma irradiation.

Claim 50 (Amended). The pharmaceutical composition of [Claim] claim 47 wherein said halogenated xanthene is Rose Bengal.